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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,852	12/10/2003	Frederick L. Hall	06666-042002 / 2895	4628

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,852	HALL ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-69 and 72-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66-69 and 72-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the rejection of the last Office Action (22 June 2006) is *withdrawn* in view of the new grounds of rejection set forth below.

Status of Application, Amendments and/or Claims

Applicant's arguments have been entered in full (11 October 2006). Claims 66-69 and 72-80 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Matter of Record

Applicant requests withdrawal of the finality of the present office action. Applicant argues that the Examiner raised new grounds of rejection, which were not necessitated by Applicant's amendment. Applicant argues that six new grounds of rejection were made, while no rejection was maintained from the previous Office Action. Applicant argues that the rejection of claims 66-69 and 72-80 for lacking enablement for all fusion peptides could have been raised by the Examiner in the previous office action, but was not.

Applicant's arguments have been fully considered but are not deemed persuasive. The Examiner will explain some of the rejections. The claims in the amendment submitted 07 April 2006 were amended from simply a fusion polypeptide comprising a collagen-binding domain and an epithelial cell proliferation-modulating agent to include various proteins. Please see claims 66, 72 and 80 from the amendment submitted 4/7/06. The Examiner made a scope of enablement rejection in the Final Office Action because the art of record and the instant specification failed to teach that some of the recited proteins affect epithelial cell proliferation and/or differentiation. Please see pages 4-6 of the previous Office Action; 22 June 2006. Claims 66-69 and 72-80 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Please see pages 3-4 of the previous Office Action; 22 June 2006. The Examiner could not have made the instant rejections based on the claims as recited before the amendment submitted 07 April 2006.

Nevertheless, finality of the final rejection has been withdrawn in view of the new grounds of rejection made below.

Withdrawn Objections And/Or Rejections

The rejection to claims 66-69 and 72-80 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (22 June 2006), is *withdrawn* in view of the amendment (11 October 2006).

The rejection to claims 66-69 and 72-80 under 35 U.S.C. 112, first paragraph, scope of enablement, as set forth at pages 4-6 of the previous Office Action (22 June 2006), is *withdrawn.*

The rejection to claims 72-79 under 35 U.S.C. 103(a) as being obvious over Hall *et al.,* U.S. Patent No. 6,955,898 B2 in view of Carlini *et al.,* Kidney International Vol. 55 pages 546-553, 1999, as set forth at pages 6-8 of the previous Office Action (22 June 2006), is *withdrawn* in view of the amendment (11 October 2006).

The rejection to claims 66, 68 and 69 under 35 U.S.C. 103(a) as being obvious over Hall *et al.,* U.S. Patent No. 6,387,663 B1 in view of Carlini *et al.,* Kidney International Vol. 55 pages 546-553, 1999, as set forth at pages 9-10 of the previous Office Action (22 June 2006), is *withdrawn* in view of the amendment (11 October 2006).

The rejection to claims 72-79 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,955,898 B2 in view of Carlini *et al.,* Kidney International Vol. 55 pages 546-553, 1999, as set forth at pages 10-12 of the previous Office Action (22 June 2006), is *withdrawn* in view of the amendment (11 October 2006)

The rejection to claims 66, 68 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,387,663 B1 in view of Carlini *et al.,* Kidney International Vol. 55 pages 546-553, 1999, as set forth at pages 12-13 of the previous Office Action (22 June 2006), is *withdrawn* in view of the amendment (11 October 2006).

Claim Rejections - 35 U.S.C. § 112, First Paragraph, Enablement

Claims 66-69 and 72-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a fusion polypeptide comprising a collagen binding domain and an epithelial cell proliferation-modulating agent, a nucleic acid sequence encoding a fusion polypeptide comprising a collagen binding domain and an epithelial cell proliferation-modulation agent and a pharmaceutical composition comprising a fusion polypeptide comprising a collagen binding domain and an epithelial cell proliferation-modulating agent with various epithelial cell proliferation-modulating agents.

The specification states that the present invention provides new compositions and methods to induce repair of epithelial tissue by specifically targeting tissue in need of such repair with a fusion polypeptide of the invention. The invention promotes

localized wound healing by providing a cell proliferation-modulation agent fused to a collagen-binding domain (page 3, lines 15-23). The specification states that the present invention provides a recombinant fusion polypeptide comprising EGF and an appropriate collagen-binding domain for enhancing the effective local concentration of EGF at the site of tissue injury thereby promoting repair of damaged intestinal mucosa in animal models and, ultimately in humans (page 8, lines 16-24). The specification states that an epithelial cell proliferation-modulating agent is any agent that can promote or inhibit cell growth or differentiation (page 10, lines 14-20). However, the specification only demonstrates epidermal growth factor (EGF) as a protein with epithelial cell proliferation activity. The examples teach the construction of a fusion protein comprising a collagen binding domain and EGF. The examples demonstrate that the fusion protein promotes epithelial cell growth in wound healing. The instant examples and the art of record fail to teach that any of the recited proteins (insulin, NGF, NGF receptor, EGF receptor, neu, inhibin a, inhibin b, Mullerian inhibitory substance, TNF receptor (type 1 or type 2), wnt-2, and HGF receptor comprising a collagen-binding domain can promote epithelial cell growth. In addition, the instant specification fails to teach an epithelial cell proliferation-modulating agent that can inhibit epithelial cell growth or epithelial differentiation. Claim 80 is drawn to a pharmaceutical composition comprising the claimed fusion proteins and thus reads on in vivo treatment. The instant examples demonstrate the efficacy of a fusion protein comprising a collagen binding domain and EGF in an animal model for experimental colitis (Figures 6 and 7). The specification fails to disclose a correlation (any working examples, animal models, etc.) between the use

of the instant invention and a treatment in subjects. An epithelial cell proliferation-modulating agent broadly encompasses any agent that can promote or inhibit cell growth or differentiation (page 10, lines 14-20). The specification teaches uses for an agent which promotes epithelial growth but fails to teach other uses. For example how would one skilled in the art use an agent having the activity of inhibiting differentiation? The instant claims recites various proteins, which are diverse from the EGF protein. It could not be predicted that the data presented in the specification would be in any way correlative with therapeutic agents comprising the instant fusion protein for in vivo treatments.

Applicant states that the Examiner concedes that a fusion protein comprising a collagen binding domain and an epithelial cell growth factor receptor promotes cell proliferation and differention. Applicant discusses TNF receptors, neu, inhibin alpha and beta, Mullerian inhibiting substance and Wnt-2. Applicant discusses the submitted references to support enablement. Applicant states that with respect to the Examiner's comment regarding receptors, it is noted that the receptors defined in the claims can be used as competitive inhibitors to decrease cell proliferation.

Applicant's arguments have been fully considered but are not deemed persuasive. The art of record and the specification fail to teach that insulin, nerve growth factor or nerve growth factor receptor can stimulate epithelial cell growth. Applicant's arguments regarding the enablement of the other proteins are not found persuasive. Cohen *et al.* fail to teach that the neu receptor induces the proliferation of epithelial cells. Matzuk *et al.* teach that inhibin alpha is a NEGATIVE regulator of gonadal stromal

cell proliferation. Behringer *et al.* teach that Mullerian inhibiting substance (MIS) actively INHIBITS the development of the mullerian ducts. **Dale *et al.* state that the data suggests that wnt-2 exspression is operational in the stroma of the normal gland and when expressed in tumor epithelium may contribute to the maitenance and possibly the generation of the transformed phenotype** (last page, the Examiner has provided the entire reference). Preliminary results from surveys of wnt-2 expression have suggested that wnt-2 may be associated with abnormal proliferation in human breast tissue (page 4320, 3rd paragraph). Dale *et al.* teach wnt-2 expression in the epithelium of 5 out of 11 infiltrating ductal tumors but was present exclusively within the fibroblast of the normal breast (page 4321, discussion, 1st paragraph). Kollias *et al.* teach that two TNF receptors are known to mediate either in cooperation or independently, **a wide spectrum of cellular responses** ranging from proliferation and differentiation to **cytotoxicity or apoptosis**. Kollias *et al.* teach that although the knowledge of the biochemistry of TNF receptor signal transduction is quite advanced, **understanding the *in vivo* functions of the two TNF receptors remain vague** (page 136, 1st paragraph). Kurada et al. teach the receptor tyrosine kinase (RTK) epidermal growth factor receptor (EGFR). Kurada *et al.* teach that RTK-mediated signaling pathways have been implicated in various cell biological processes such as cell proliferation, cell differentiation and cell survival. **These receptors are activated by ligand binding** and in turn activate intracellular signaling pathways (page 239, abstract and 1st-3rd paragraph, the Examiner has provided the entire reference). In addition, regarding the use of receptors, the recited protein receptors must form proper structure

and be activated by its ligand. The specification fails to teach that any of the recited receptors can be expressed as a fusion polypeptide and activated by its ligand. The specification fails to teach that its ligand will be in an effective concentration at the targeted tissue site. Lastly, as was stated above, the instant specification fails to teach an epithelial cell proliferation-modulating agent that can inhibit epithelial cell growth or epithelial differentiation. The instant specification fails to teach that the receptors defined in the claims can be used as competitive inhibitors to decrease cell proliferation. It fails to teach the assays to discern an inhibition of epithelial cell growth or epithelial differentiation.

Due to the large quantity of experimentation necessary to determine how to use the recited proteins other than as a protein agent having the activity of stimulating epithelial cell proliferation, the large quantity of experimentation necessary to show a correlation between the recited pharmaceutical compositions and treatment in a subject and the large quantity of experimentation necessary to express a functional receptor protein; the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same; the complex nature of the invention; the contradictory state of the prior art which fail to teach epithelial cell proliferation activity for the recited proteins; the unpredictability of what biological activities the wnt-2 and TNF receptor proteins may have; undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
11/16/06

Marianne P. Allen

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